Remarks

Claims 7-9 and 13-49 are pending and under examination in the instant application. Claims 13-27 and 29-32 are withdrawn from further consideration pursuant to the provisions of 37 CFR §1.142(b), as being drawn to nonelected inventions.

Claims 40 and 45-49 are rejected.

Applicants acknowledge that Section 9 of the Office Action indicates that Claims 7-9, 28 and 33-39 are found allowable. This Amendment does not involve any issue of new matter. Therefore, entry of this Amendment is respectfully requested.

Claim Amendments

Claims 40-47 have been amended. Claims 40-47 have been amended to correct minor grammatical errors and to make the language of the claim set more consistent. In addition, the claims have been amended to recite a "recombinant antibody" instead of the original term a "monoclonal antibody." Support for this amendment can be found in paragraph [0357] of US 2004/0133357 (USPTO publication of the instant application).

Claim Objections

Section 9 of the Office Action indicates that Claims 41-44 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Because Applicants believe that the subject matter recited in the base claim (i.e., Claim 40) is patentable, they have chosen not to rewrite Claims 41-44 in independent form at this point in time. Applicants respectfully direct the Examiner's attention to the arguments provided below which address the alleged lack of enablement of the subject matter of Claim 40.

Claim Rejection Under 35 U.S.C. §112, first paragraph

The Office Action indicates that Claims 40 and 45-49 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to enable one of skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner stated that the specification allegedly does not reasonably provide enablement for anti-VEGF antibodies that do not consist of all six CDRs (as in claims 40 and 45-47) or a VH domain or a VL domain (as in claims 48 and 49). The Examiner stated that it is unlikely that

humanized antibodies which do not contain all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their correct spatial orientation have the requisite VEGF binding function. This interpretation leads the Examiner to conclude that the specification does not enable any person skilled in the art to make or use the invention commensurate in scope with the rejected claims.

Claims 40 through 47 Satisfy the Enablement Requirement of 35 U.S.C. §112

Applicants respectfully traverse the outstanding rejection of Claims 40 (as well as its dependent Claims 41-44) and Claims 45-47 and contend that the specification in combination with what was known in the art at the time the subject application was filed does enable one skilled in the art to make and use an antibody comprising a defined V_H sequence or V_L sequence as set forth in claims 40 and 45-47.

Applicants respectfully disagree with the Examiner's interpretation of the subject matter recited in Claims 40 through 47. More specifically, Applicants disagree with the Examiner's statement that Claims 40 through 47 are recite subject matter which lack "all of the necessary elements required for the antigen-binding property of an antibody" (Office Action, page 3).

It is apparent from the above-stated rejection that the Examiner is misconstruing the subject matter of Claims 40 (as well as its dependent Claims 41-44) and Claims 45-47. The preamble of Claims 40 and 45-47 indicated that all of the rejected claims are directed to:" [a] monoclonal antibody that specifically binds to a human VEGF." Based on the disclosure provided in the specification, and on the knowledge of one of skill in the art, the term "monoclonal antibody" refers to a heterodimeric molecule that consists of six CDRs. The art teaches, and the disclosure in the specification is consistent with, this well-established definition and with the fact that the six CDRs consist of three CDRs from a V_L domain and three CDRs from a V_H domain.

The rejected Claims are each drafted to define a genus of anti-VEGF antibodies which share a common set of three CDRs contributed by a particular light chain variable domain (V_L) (Claims 40, 45 and 47) or a particular set of CDRs contributed by a heavy chain variable domain (V_H) domain (Claims 41 and 46). Therefore, each of the claims recites a genus of heterodimeric antibodies comprising six CDRs which are unified by 1) a common specificity for VEGF and 2) a common structural feature attributed to the presence of a defined common V_L or V_H domain that contributes three of the six CDRs to each of the

antibodies. The data provided in Figures 2A-2C and Figure 3 documenting the affinity analysis of a panel of anti-VEGF antibodies comprising the V_L and V_H domains of the invention provides support for the VEGF specificity of the disclosed antibody and the sequences provided in the sequence listing and presented in the alignment profile of Figure 1 provide support for the common structural feature of the V_L and V_H domains of the invention.

This explanation of the claimed subject matter is supported throughout the specification in a series of paired paragraphs which repeatedly indicate that the invention essentially provides collections of preferred V_L and V_H sequences (e.g. domains) which are intended to be used in a mix and match combination strategy with each other to provide anti-VEGF monoclonal antibodies. It is also supported by the language of Claims 33 through 36 which define anti-VEGF antibodies as comprising particular pairs of V_L and V_H domains.

For example, see paragraphs [0015] and [0016] of the published application (US2004/0133357). Paragraph [0015] indicates that "a monoclonal antibody is provided that specifically binds to a human VEGF and has a V_L comprising..." (a particular amino acid sequence). Paragraph [0016] indicates that the preferred V_L sequence provided by the invention and described in paragraph [0015] "may be combined with the preferred V_H sequence or V_H of other antibodies provided that the antibody so produced binds to the human VEGF with a desired affinity (emphasis added)." The underlined part of the sentence quoted from paragraph [0015] provides guidance regarding how to select a binding pair member for the defined member of the genus.

Similar sets of paired paragraphs describing the disclosed V_L and V_H sequences and their contemplated use as components of a heterodimeric anti-VEGF "monoclonal antibody" occur throughout the specification. For example, paragraphs [0020] and paragraph [0021] describe preferred V_H sequences (domains) and paragraph [0021] indicates their intended use in combination with V_L sequences to produce anti-VEGF antibodies.

Applicant's position that the claimed "monoclonal antibodies" comprise heterodimeric molecules comprising six CDRs is also supported by the text provided in paragraphs [0051] and [0052] of the specification which define the V_L and V_H pairings of the optimized (i.e. variant) antibodies that were assayed to produce the data summarized in Figures 2 and 3 of the disclosure. For example, see lines 10-15 of paragraph [0052] of US 2004/0133357), which indicates that the anti-VEGF antibodies of the invention comprises particular defined V_L and V_H pairings to produce the antibodies of the invention. Furthermore, the disclosure provided in Example 4 (paragraph [0468]) clearly teaches that

the anti-VEGF antibodies of the invention were expressed as scFvs including a V_H fragment and a V_L fragment connected by a linker.

In order to advance the prosecution of the subject matter of Claims 40 through 47, Applicants have amended the language of the rejected claims to recite "recombinant antibody" as opposed to "monoclonal antibody." Support for this amendment can be found in paragraph [0357] of US2004/0133357 which provides a definition for the term "recombinant antibodies" which make it clear that the antibodies encompassed by Claims 40-47 all comprise six CDRs. This is apparent from the fact that the term is defined as fully assembled antibodies, Fab fragments, Fv fragments or single chain antibodies. Applicants note that on page 3 of the outstanding Office Action, the Examiner has acknowledged that the specification is enabling for antigen-binding fragments of antibodies comprising six CDRs (three from a VH domain and three from a VL domain).

Applicants maintain that claims 40 and 45-47 satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the outstanding enablement rejection.

Claims 48 and 49 Satisfy the Enablement Requirement of 35 U.S.C. §112

Applicants respectfully traverse the outstanding rejection of Claims 48 and 49 and contend that the specification in combination with what was known in the art at the time the subject application was filed does enable one skilled in the art to use an antibody variable domains comprising a structurally optimized V_L or V_H domain with a predetermined binding specificity attributed to its parental antibody source. As indicated in paragraph [0410] of US 2004/0133357 the parental antibody of the V_L and V_H domains of the invention is a murine anti-VEGF antibody. Therefore, Applicants are not attempting to produce antibodies comprising less than all six CDRs that bind VEGF de novo.

The instant specification provides numerous V_L (SEQ ID NOS: 2-54) and V_H (SEQ ID NOS: 57-110 and 285-310) domains derived from a parental antibody having specificity for VEGF using the *in silico* design methodology described in Example 1 of the specification. A skilled artisan will readily recognize that the V_L and V_H domains recited in claims 48 and 49 represent building blocks that can be used to produce optimized anti-VEGF antibodies.

In response to the Examiners statement that "the specification does not provide any method of identifying a humanized VH when only a humanized VL is disclosed" (Office Action, page 5), Applicants respectfully direct the Examiner's attention to paragraph [0445]

and [0046] of US 2004/0133357 which indicates that a hit variant library (produced using degenerate oligos) was cloned into a phage display system and the phage-displayed antibodies were selected based on their binding to immobilized VEGF... The subsequent sentence in the referenced paragraph teaches that:

> [t]he library was installed into a phage display vector pABMD12 in which the VH of anti-VEGF was replaced by the library. As a result, VL and a variety of VH generated from the library would pair to form a functional ccFc of anti-VEGF.

As noted in the last Amendment, and acknowledged by the USPTO, as of the filing date of the subject application, methods were known in the art for producing antibodies that bind a specific antigen by using a specific VL (or VH) and screening a library of the complimentary variable domains (see Portolano et al. (1993) *The Journal of Immunology* 150: 880-887 (copy attached to Amendment filed on Jan. 15, 2008 as Exhibit 2); see also Clark et al. (1991) *Nature* 352: 624-628 (copy attached Amendment filed on Jan. 15, 2008 as Exhibit 3)). It is well-established that a patent application does not need to expressly teach what is well known in the art.

Summary

For the reasons set forth hereinabove, Applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and objection, and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

Respectfully submitted,

By _____

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